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ARTHUR W. ALLEN

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# THROMBOSIS AND EMBOLISM

## *A Preliminary Report on the Comparative Results of Femoral Vein Interruption and Dicumarol Therapy**

ARTHUR W. ALLEN

Chief, East Surgical Service, Mass. General Hospital, Boston
Lecturer in Surgery, Harvard Medical School.

CONSIDERABLE progress has been made on the thrombo-embolic syndrome during the past decade. It has long been established that there is a direct association between thrombus formation in the deep veins of the legs and pulmonary embolism. Evidence points to the leg-veins as the source of these thrombi in approximately 95 per cent of the cases. Patients ill enough to remain in bed, following surgical procedures, medical disorders, parturition, or trauma, are, under certain conditions prone to develop thrombosis in the leg veins. Occasionally, thrombophlebitis occurs in ambulatory individuals without known infection or illness. Instances of sudden death in a patient apparently making a satisfactory convalescence are familiar to everyone. Prolonged invalidism following phlegmasia alba dolens has long been one of the serious sequelae of parturition and surgery.

Efforts have been made to reduce the incidence of complications

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from inflammatory reaction in and about the deep veins and lymphatics of the legs. Contributions on the subject have dealt with etiological factors such as trauma, infection, protein levels in the blood and stasis in the veins. Too much stress has been placed on the origin of these thrombi in the pelvic veins following parturition, gynecologic operations, and prostatectomy. This, I believe, has delayed progress on the more serious condition of thrombosis in the deep veins of the legs. Posture, exercises, better surgical principles, and other factors have reduced the incidence of thrombosis and embolism. In spite of these precautions, there still remain definite problems to be solved in this field.

Homans[1] has called attention to "bland thrombosis" of the leg veins and Ochsner and DeBakey[2] have emphasized and confirmed this phenomenon and suggested the term "phlebothrombosis" to distinguish this condition from the usually recognized inflammatory thrombophlebitis. The most important reason for distinction in these two types of thrombosis lies in the fact that the non-inflammatory thrombus is loosely attached to the vein and is the chief source of serious pulmonary infarction. Part or all of a complete cast of the long deep veins of the legs may be deposited in the pulmonary arteries in a sudden manner causing death within a few minutes. If the detached thrombus is less extensive, a typical infarct in the lung occurs. It is well known on the other hand that in the fulminating, acute, inflammatory thrombosis of the leg veins associated with pain, fever and swelling of the leg fatal embolus is less likely. This is probably due to the fact that, under these circumstances, the thrombus is firmly attached to the lumen of the veins by inflammatory reaction.

The mechanism of the embolic phenomenon has recently been discussed by Chapman and Linton.[3] They have demonstrated that straining, as in defecation, superimposed on inspiration, changes the venous pressure in a manner favorable to the emptying of the veins in the legs. It is well known that many fatal emboli occur during the use of the bed pan.

We have frequently observed that, seemingly unquestionable bland thrombosis has often gradually changed into thrombophlebitis. Whether this is a transitional type of the disease, it is difficult to determine. I am sure that we do have the two typical extremes of the non-inflammatory phlebothrombosis on the one hand and the acute inflammatory thrombophlebitis on the other. In the former or more dangerous type from the

standpoint of embolism, we have little general reaction, little if any swelling of the leg and a minimum of tenderness or pain. The diagnosis in this variety is most often made after infarct has taken place. In true phlegmasia alba dolens, we have an acute onset of pain and swelling in the leg associated with fever, leukocytosis and elevated sedimentation rate. In this type, the diagnosis is obvious and easy and emboli to the lungs rarely occur. Between these two extremes we have all gradations of the disease. Bland thrombosis will often produce dilation of the superficial veins of the leg and foot—a slight cyanosis and a mild discomfort in the calf muscles on dorsiflexion of the foot (Homans' sign) and perhaps a slight swelling above the ankles. If infarct occurs with or without chest pain, there will be a typical mild elevation of temperature, pulse, and respiration at the same recording on the clinical chart. One needs nothing more than these minor indications for the institution of proper therapy. Under these conditions, whether the femoral vein is interrupted or not, there may follow a gradual increase in swelling, pain and tenderness in the leg, with more or less general reaction as observed in the typical inflammatory form. It is my belief that this transition from a bland to an inflammatory process may be more common in colder, damper climates than in warmer, drier zones.

The fact that our peak incidence of thrombosis and embolism occurs in the winter months (33 per cent) and our lowest incidence during the summer (19 per cent) would seem to support this contention.[4] Also, it would appear that fewer of the cases of phlebothrombosis develop into thrombophlebitis in New Orleans than in Boston. Furthermore, it seems that thrombophlebitis may run a milder course and is more amenable to sympathetic bloc in Ochsner's hands than in ours. There seems to be little if any variation in the type of patients admitted to the white wards of the Charity Hospital in New Orleans and to the Massachusetts General Hospital.

One of the factors of great importance in the discussion of this subject is the age of the patient. In our clinic only 5.7 per cent of the patients with thrombosis and embolism were under 30 years of age—an additional 12 per cent were between 30 and 40, leaving a total of 82.3 per cent above the age of forty. The largest group of patients with thrombosis of the leg veins was in the fifth decade or 25.3 per cent and the next in the sixth decade 22.9 per cent. Actually these figures begin to be slightly misleading at this point since the peak of admissions to the

hospital is during the fifth decade. The ratio of patients treated to the number with complications of thrombosis and embolism rises with the age of the patient. In an effort to determine why we were recognizing a greater percentage of this phenomenon in our clinic, a comparative analysis revealed that the patients admitted in 1943 averaged eight years older than those treated in 1930. The relative frequency of thrombosis and embolism in the older age group became so apparent that a number of the aged were protected from embolism by prophylactic femoral vein interruption.

There are two definite methods of preventing fatal embolus available at this time. The use of anti-coagulant drugs such as heparin and dicumarol are effective if properly used and there are strong advocators of this method.[5, 6, 7, 8] There are definite contraindications to the use of these drugs and the greatest care must be exercised in this regard. Heparin is expensive but has the advantages of rapid effect and of being inactivated quickly by protamine. It is of tremendous value as an adjunct to dicumarol during the lag period of the first 48 hours of treatment. Also, it is important after femoral vein interruption if minor infarcts occur from uninterrupted veins. Dicumarol has been used to some extent by Butsch and Stewart[6] preoperatively but the majority of pioneers in this field have felt it safer to use it after operation. Interruption of the long veins of the leg is the other chief method at our disposal at this time.

Up to October 1, 1945, we have interrupted the femoral veins on 816 patients at the Massachusetts General Hospital. These have been done for the following reasons:

(a) Definite signs and symptoms indicating thrombosis in the leg veins; 47.3 per cent.

(b) Signs of infarct in the lungs; 34.4 per cent.

(c) Prophylactic interruptions in patients whose age and acute disorder would indicate a high probability of thrombosis during their treatment; 18.3 per cent.

There has been an increasing tendency to interrupt the veins in both legs if any is done. This is due to the fact that we have frequently found thrombi on the supposedly normal side. We are further reassured of the safety of this procedure since interruption of the normal or uninvolved vein produces no appreciable disturbance to the patient. Swelling of the extremity after interruption of a thrombosed vein will vary some-

Table I—INDICATIONS FOR FEMORAL VEIN INTERRUPTION

| | *1937-1942* | | *1943* | | *1944* | | *1945 (¾)* | |
|---|---|---|---|---|---|---|---|---|
| Leg signs as first symptom | 120 | 59.0% | 93 | 56.3% | 117 | 41.8% | 57 | 33.7% |
| Chest pain as first symptom | 82 | 41.0% | 57 | 34.5% | 91 | 32.5% | 50 | 29.6% |
| Prophylactic interruption | 0 | 0 | 15 | 9.2% | 72 | 25.7% | 62 | 36.7% |
| | 202 | | 165 | | 280 | | 169 | |

Table II—FEMORAL VEIN INTERRUPTION

Massachusetts General Hospital—1937 to October 1, 1945

| | *Patients* | *Veins* | *Unilateral Interruption* | | *Bilateral Interruption* | |
|---|---|---|---|---|---|---|
| 1937-1942 | 202 | 280 | 124 | 61.0% | 78 | 39.0% |
| 1943 | 165 | 299 | 31 | 19.0% | 134 | 81.0% |
| 1944 | 280 | 554 | 6 | 2.1% | 274 | 97.9% |
| 1945 | 169 | 335 | 3 | 1.8% | 166 | 98.2% |
| Total | 816 | 1468 | | | | |

what depending on the duration, the extent, and the inflammatory element in the thrombosis. If the vein is interrupted prophylactically, there is so little post-ambulatory swelling that it is hardly noticeable. In the past two years less than 2 per cent of the patients have had unilateral interruption if any is done and these were in the private wards.

These operations have been done almost entirely by the resident staff. There has been no fatality as a result of the venous interruption. There has been only one death from massive embolus following femoral vein interruption. This embolus came from the profunda femoris vein 8 days after the superficial femoral vein had been ligated. Infection has occurred in less than 2 per cent of the wounds. This is amazing when the majority of the operations have been done more or less as an emergency on a previously unprepared field. Complete change of instruments, gloves, and drapes are used on the second side. Lymphorrhea has occurred in a few cases. This complication is reduced to a minimum if the incision is kept parallel to the pulsating femoral artery with as little lateral dissection as possible. Postoperative edema has been variable and in no incidence disabling. It appears that some of the cases are operated upon so early in a true thrombophlebitis and before the classi-

cal picture of full-blown phlegmasia alba dolens develops that the progress of this disease is definitely altered. This probably accounts for the variation in post vein interruption swelling. There has been only one instance of postphlebitic varicose ulcer. The average period of hospital stay after vein interruption has been approximately nine days. When one considers the prolonged invalidism commonly seen in the conservative methods of treatment for thrombophlebitis with the late sequelae of edema, varicosities, and ulcerations, it would seem that early radical treatment represented progress.

Although there has been some difference of opinion in our group concerning the site of phlebotomy and interruption of the veins of the legs and a considerable number of common femoral veins have been ligated, I am definitely of the opinion that the best routine is to open the superficial femoral vein, remove the thrombi if any exist by suction, and then completely divide the vein between ligatures previously placed. It is felt by some that if the profunda femoris is also thrombosed the interruption should be done above this level. Since there are numerous radicals entering the vein just proximal to its major bifurcation, the dissection is tedious and troublesome hemorrhage may occur. Also, it has been pointed out that very serious acute edema of the leg may on occasion result from interruption of the common femoral.[9] We have had only one fatal embolus arising from the profunda femoris after superficial femoral vein occlusion. This, I believe, is a small price to pay for the added safety and ease of procedure when the superficial femoral just below the profunda is selected as the site of interruption.

Inasmuch as we had a definite background of experience with femoral vein interruption for thrombo-embolic disease, it was felt that comparative studies, using dicumarol on similar patients, were indicated. As we have two identical surgical services at the Massachusetts General Hospital, it seemed that these observations might be of value. It was evident from our previous studies that fatal embolism was rare and the morbidity from thrombosis was less in patients under 40 years of age. Also, if infarct or leg signs occur in this age group, proper treatment can nearly always be instituted in plenty of time to prevent catastrophy. For these reasons, no change was made in the handling of this group of patients. In those patients between the ages of 40 and 65 on the East Surgical Service that had no contraindication to the use of dicumarol, prothrombin times were determined and 200 mg. of

the drug administered on the second or third postoperative day. If a definite rise in the plasma prothrombin level did not occur or if the patient could not be mobilized by the time a normal level was reached, a second dose of the same size was to be given. On all patients over 65 years of age who were to undergo operative procedures that prevented early rising, prophylactic femoral vein interruption was practiced. Through the coöperation of L. S. McKittrick (acting chief of the West Surgical Service) the West Surgical patients were used as controls. Pre- and post-operative plasma prothrombin times were obtained on both services in the middle age group.

Doubtless there will be criticism of the small dose of dicumarol used since most reports would indicate that a much larger amount of the drug is necessary to obtain the desired elevation in the prothrombin time. We had had some experience with the variability of its action and had no desire to precipitate serious complications as a result of overdosage. We also knew that the prothrombin time could be elevated in many instances by one, and, if this was not effective, by a second small dose. George Van S. Smith[10] of Boston has used dicumarol in small doses postoperatively in a large group of gynecologic patients and reported informally on his experience. We hoped that we could work out a formula that would make this agent safely available, without the need of so much time consuming laboratory work. It is inevitable that such drugs will be used empirically and already catastrophes have been reported when dicumarol was administered incorrectly and without control.[11] Almost certainly there are many similar but unrecorded episodes.

Contraindications to the use of dicumarol are numerous but obvious. Doubtless many of these are somewhat theoretical, particularly when small doses are used (Table III). Inasmuch as the thrombo-embolic syndrome is not common before the fifth postoperative day, it was expected that these studies might show some regularity in prothrombin time elevation after operation. This was not the case, however, since rarely was there any difference in the pre- and post-operative levels. We were interested to find that approximately 2 per cent of patients in Group II, who had no other contraindication to dicumarol, already had an elevated prothrombin time pre-operatively. We considered it unsafe to use dicumarol if the level was over 25 seconds. One patient with an elevation of 26 seconds did receive a dose of 200 mgms. of dicumarol,

Table III—CONTRAINDICATIONS TO DICUMAROL THERAPY—Age 40-65

1. Liver disease including jaundice
2. Kidney disease
3. Diabetes
4. Hemorhagic diathesis, purpura, hemophilia, etc.
5. Hyperthyroidism
6. Arthritis. Patients receiving aspirin
7. Premature arteriosclerosis
8. Hypertension, especially patients for splanchnisectomy
9. Chest cases
10. Patients with plasma prothrombin above 25 seconds
11. Multiple stage operations (planned)
12. Minor surgical procedures and cases suitable for early ambulation

Table IV

Of 528 patients admitted to the East Surgical Service from January 1 to September 30, 1945, between the ages of 40-65, 101 received dicumarol. The remaining 427 patients did not receive it for the following reasons:

| | |
|---|---|
| Hospitalized for minor procedure (includes early ambulatory cases) | 48.0% |
| Admission for study, no operation performed | 19.5 |
| Liver disease | 6.0 |
| Hypertension | 6.0 |
| Chest cases | 6.0 |
| Diabetes | 3.5 |
| Hyperthyroidism | 3.5 |
| Excessive bleeding at operation | 3.5 |
| Plasma prothrombin time elevated above 25 seconds | 2.5 |
| Arthritis | 1.5 |
| Total | 100.0% |

in error, without harm. No thrombosis or embolism occurred in these individuals with abnormally high levels but we were not impressed by any certainty of thrombosis in those with abnormally low levels.

From Jan. 1 to Oct. 1, 1945, 101 patients in age group II received dicumarol postoperatively. This represents only 19 per cent of the patients in this Group. The contraindications to its use in the remaining 81 per cent of patients are shown in Table IV; ninety-one patients had only one dose of 200 mgms. and ten had two doses; sixty-two of those receiving one dose had a satisfactory rise of the plasma prothrombin

Table V—POSSIBLE DICUMAROL COMPLICATIONS

| *No.* | *Age Sex* | *Diagnosis* | *Operation* | *Dicumarol* | *Prothrombin Time (secs.)* | *Complication* |
|---|---|---|---|---|---|---|
| 54491 E.S. | 60F | Lipoma ascending colon | Rt. Colectomy. Ileocolic anastomosis | 200 mgm. 3 day p.o. 200 mgm. 6 day p.o. | Pre-op. 13 5 days p.o. 18 8 days p.o. 21 | On 8th p.o. day developed ecchymosis at site of hypodermic injections. Moderate hemorrhage from anastomosis. |
| 478129 R.L. | 47F | Ca. Breast | Radical mastectomy | 200 mgm. 2 day p.o. | 4 days p.o. 33 | Moderate sanguineous drainage from wound post-operatively. |
| 24562 S.C. | 40F | Cystocele Rectocele | Repair | 200 mgm. 2 day p.o. 200 mgm. 5 day p.o. | 3 days p.o. 22 7 days p.o. 23 9 days p.o. 25 | Some bleeding via catheter 4 days post-operatively. |
| 9961 S.W. | 41F | Fibroid Uterus | Hysterectomy Perineorrhaphy | 200 mgm. 3 day p.o. | Pre-op. 21 2 days p.o. 24 8 days p.o. 30 | Developed small hematoma in wound on 14th post-op. day. |
| 478674 M.B. | 48F | Cystocele | Cystocele Repair | 200 mgm. 2 day p.o. 200 mgm. 8 day p.o. | Pre-op 21 5 days p.o. 21 9 days p.o. 32 | On 11th day post-op. developed infected hematoma at vaginal apex of wound with bloody discharge. Temperature rise. Urticaria. |
| 492336 A.F. | 50M | Stenosing duodenal ulcer | Subtotal gastrectomy | 200 mgm. 2 day p.o. | 5 days p.o. 20 | Patient died suddenly on 10th post-op. day. Possible cerebrovascular accident. No embolus at autopsy. Permission to examine brain refused. |

No patient required Vitamin K therapy to combat hypoprothrombinemia.

Patient #54491 was given a transfusion for hemorrhage from anastomosis.

Table VI—THROMBO-EMBOLIC PHENOMENA IN THE DICUMAROL TREATED GROUP

| *No.* | *Age Sex* | *Diagnosis* | *Operation* | *Dicumarol* | *Prothrombin Time (secs.)* | *Complication* |
|---|---|---|---|---|---|---|
| 30404 R.H. | 64M | Ca. Cecum | Right Colectomy | 200 mgm. 3 days p.o. | Pre-op. 21<br>3 days p.o. 21<br>6 days p.o. 22<br>7 days p.o. 22 | Developed phlebothrombosis 14th day p.o. Superficial femoral veins interrupted. X-ray "suggestive of infarct." |
| 354772 E.A. | 49F | Cholecys-titis | Cholecys-tectomy | 200 mgm. 2 days p.o. | 2 days p.o. 21<br>4 days p.o. 31<br>6 days p.o. 19 | Developed symptoms of thrombo-phlebitis on 10th p.o. day. Superficial femoral veins interrupted. X-ray showed "atelectasis or infarct." |
| 246209 I.C. | 43F | Cholecys-titis | Cholecys-tectomy | 200 mgm. 2 days p.o. 200 mgm. 8 days p.o. | Pre-op. 21<br>1 day p.o. 21<br>11 days p.o. 20 | Minor episode of calf tenderness. Subsided in a short time. Femoral vein interruption 2 years previously. |

time while 29 had little or no measurable response; five of those receiving a second dose had a desirable rise while the other five had none. The highest elevation following one dose was 60 seconds and the highest rise with two doses was 45 seconds. None of these had a hemorrhagic reaction requiring a massive dose of 60 mgms. of synthetic vitamin K. One patient had a transfusion following a moderate hemorrhage from the suture line in an ileocolic anastomosis on the eighth postoperative day. It is interesting to note that she had no measurable effect from dicumarol. All of the possible complications of the dicumarol treated group are analyzed in Table V. We are not convinced that any of these undesirable sequelae are due to the effect of dicumarol. Such complications occur in patients of this type when dicumarol has not been used. The patient who died more or less suddenly on the tenth postoperative day might have had a cerebrovascular accident but since permission to examine the brain was refused by the family, we cannot do more than say that no other cause of death was found at autopsy.

The three instances of thrombo-embolic phenomena occurring in the dicumarol treated group are analyzed in Table VI. Two of these patients had no appreciable change in the plasma prothrombin time as a result of dicumarol. One of these had had bilateral femoral vein interruption at a previous admission two years before. One patient had a satisfactory rise to 31 seconds on the fourth postoperative day. All three of these patients were ambulatory for some time before they developed signs of thrombosis or infarct. It is quite probable that repeated small doses or larger amounts of dicumarol would have prevented thrombosis in these patients, particularly in the two who did not have a previous history of thrombosis.

Some patients have received heparin and dicumarol therapy following femoral vein interruption in an attempt to diminish the extension of thrombosis in other veins and thus prevent or diminish further infarcts. Also, a few patients have been given dicumarol in an attempt to shorten the course of thrombophlebitis after femoral vein interruption. None have been treated recently in our clinic for the thrombo-embolic phenomena by anticoagulant drugs alone, since in earlier reports we have shown that this method was less satisfactory.[12] The convalescent period is greatly reduced by a concomitant interruption of the chief source of fatal emboli. The combination of methods has

Table VII—COMPARATIVE DATA: EAST SURGICAL SERVICE USING DICUMAROL IN GROUP II AND PROPHYLACTIC FEMORAL VEIN INTERRUPTION IN GROUP III—WEST SURGICAL PATIENTS USED AS CONTROLS

M.G.H.—Jan. 1 to Oct. 1, 1945

| | | *I* *1-39 yrs.* | *II* *40-64 yrs.* | *III* *65 yrs.* | *Total* |
|---|---|---|---|---|---|
| EAST SERVICE (Dicumarol) | Postoperative Phlebitis | 4 | 3 | 2* | 9 |
| | Prophylactic | 0 | 3 | 50 | 53 |
| | Admissions | 448 | 528 | 165 | 1141 |
| WEST SERVICE (Control) | Postoperative Phlebitis | 7 | 14 | 11 | 32 |
| | Prophylactic | 0 | 0 | 0 | 0 |
| | Admissions | 458 | 562 | 177 | 1197 |

* Developed phlebitis requiring vein interruption before prophylactic interruption had been done.

also been found satisfactory by Parsons.[13]

In the control Group II, there were fourteen instances of thrombosis requiring femoral vein interruption (Table VII). These patients were comparable in every respect to those in the same age group receiving dicumarol.

In Group III, there were fifty patients subjected to prophylactic femoral vein interruption and in none of these did any thrombo-embolic episode occur. One patient of sixty-eight with extensive carcinoma of the rectum, widespread metastasis and obstruction, reacted badly to colostomy done under novocaine anesthesia. Her plasma prothrombin time was 24 seconds. She would have had prophylactic femoral vein interruption if her condition had permitted, on the basis of our outlined management of this age group. It did not seem feasible to undertake it and there were no signs of phlebothrombosis. She died suddenly on the fourth postoperative day of a massive embolus from the veins of the right leg.

In the Control Group III, there were eleven instances of thrombosis and embolism. One patient of sixty-eight had a large papillary cystadenoma of the ovary removed and was ambulatory on her second postoperative day. She presented no signs of phlebothrombosis although she had had a mild febrile course during her first week after admission,

thought to be due to necrosis in her pelvic tumor. Her chart had been normal for 3 days prior to laparotomy. Sudden death occurred on the 4th postoperative day and postmortem examination revealed a massive pulmonary embolus arising from the leg veins. In all the other patients in this group, thrombectomy and femoral vein interruption were successfully carried out after signs of thrombosis or infarct were recognized.

There was one other embolic death on the surgical services in the nine month period covered by this report. A man of 45 was being studied for carcinoma of the lung. No operative procedures had been carried out. No evidence of phlebothrombosis had been noted. On the 9th hospital day, he expired suddenly. Autopsy revealed massive pulmonary embolism, arising from the veins of the right leg, oatcell carcinoma of the lung with metastasis to the liver, pancreas and lymph nodes with perforation of the latter into the esophagus.

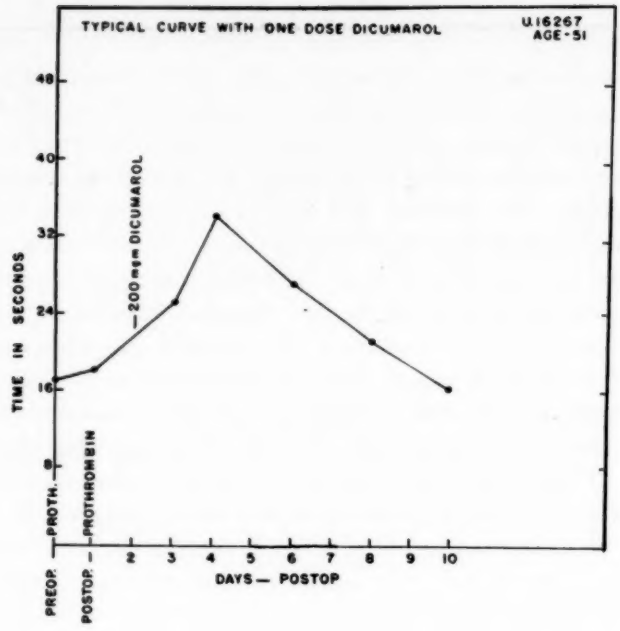
It was felt that we should establish, if possible, the most satisfactory method to our chemists of plasma prothrombin time determinations. Therefore, comparative results were carried out simultaneously on four modifications. The Quick[14] and the Shapiro[15] methods were used both with the undiluted and the diluted serum. Although the variation between the normal and the elevated prothrombin time is exaggerated by the dilute methods and the effect of the drug may be more quickly determined by this modification, there is probably little choice between them. Charts 1, 2, 3, and 4 show the curves obtained during our studies. Our chemists are somewhat inclined to like the undiluted method of Quick better and feel that it gives fewer variations than that of Shapiro. It is obvious that the curves parallel each other with a fair degree of regularity.

This is a time consuming laboratory test and must be done by one of experience. It seems unlikely that any of the present methods could be relied upon unless the technician has been well trained in this specific procedure and did these tests often.

## Summary and Conclusions

1. Thrombectomy and bilateral superficial femoral vein interruption is a safe and satisfactory method of treating early thrombophlebitis. It is a reliable method of preventing pulmonary embolism after signs, symptoms, or clinical chart show evidence of phlebothrombosis.

2. Prophylactic bilateral superficial femoral vein interruption is a


TYPICAL CURVE WITH ONE DOSE DICUMAROL
U.16267
AGE-51
TIME IN SECONDS
48
40
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24
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200 mgm DICUMAROL
PROTH.
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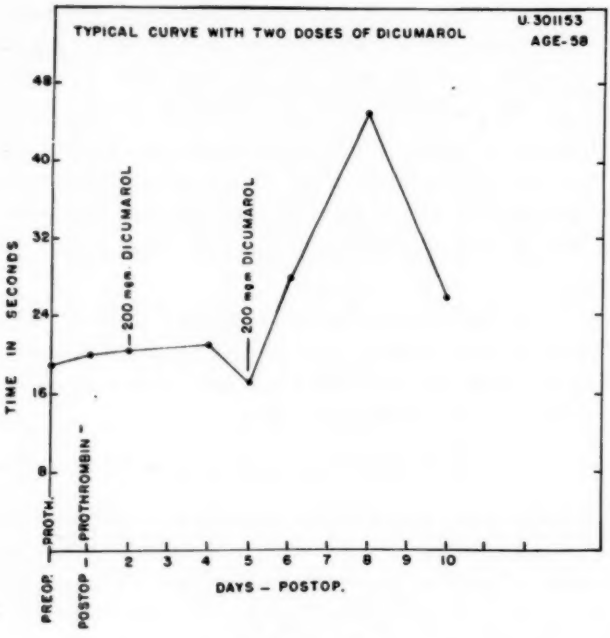
DAYS — POSTOP


TYPICAL CURVE WITH TWO DOSES OF DICUMAROL
U.301153
AGE-58
TIME IN SECONDS
48
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200 mgm DICUMAROL
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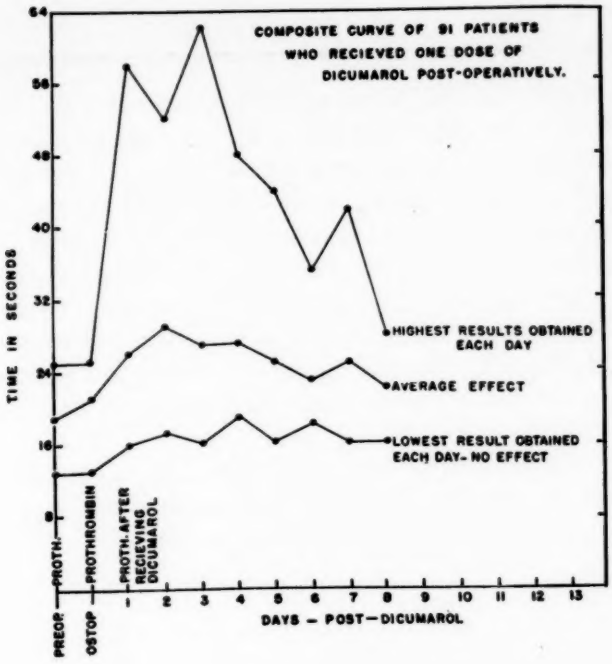
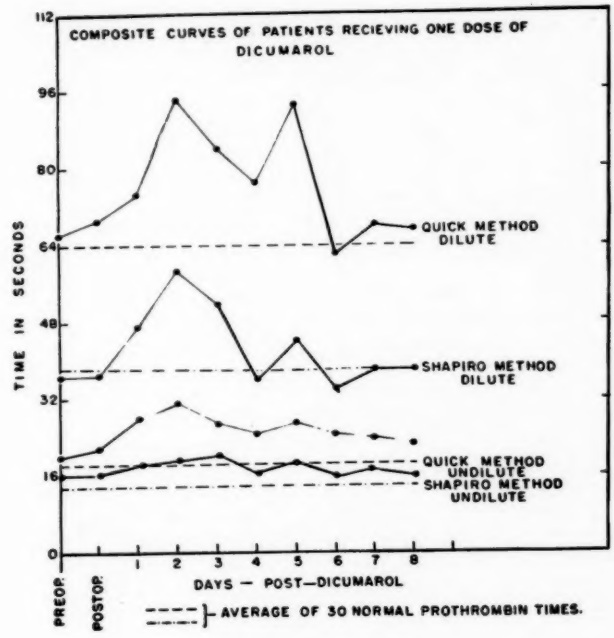
DAYS — POSTOP.

CHARTS I & II




**CHARTS III & IV**

safe and harmless procedure and prevents postoperative thrombosis and embolism. It is particularly suitable in the older age group of patients.

3. Common femoral vein interruption is not recommended in spite of one fatal embolus, occurring in our series, from the profunda femoris vein after superficial femoral interruption. Serious sequelae can occur under certain circumstances from common femoral vein occlusion. The technical difficulties far outweigh any added protection to the patient.

4. Dicumarol in small doses appears to be safe and effective in selected patients as a preventive against thrombosis and embolism. It is useful in conjunction with femoral vein interruption after thrombosis occurs.

5. Careful laboratory observations on the plasma prothrombin time preoperatively and after dicumarol administration are imperative for the safety of the patient when this drug is used.

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# SEDATION AS A TECHNIQUE IN PSYCHOTHERAPY*

LT. COL. ROY R. GRINKER, M.C.

Army Air Forces

## *Introduction*

As knowledge of the human mind in health and sickness developed, progress toward rational and effective treatment in the field of psychiatry has been associated with fluctuating emphasis on the use of sedation. Although Pinel in France and Tuke in England removed the chains from the insane in 1792, mechanical restraint in the form of strait-jackets and other devices were still used, but as curative instruments rather than as punitive measures. These were soon superseded by another form of restraint induced by drugs and dignified by the term "chemical restraint."

In light of our present knowledge it is probable that these drugs were even more harmful than the physical methods previously employed. Their administration was frequently deputized to ignorant attendants whose main motivation was to keep the patients quiet and their own nights undisturbed. One infamous hospital kept on the wards a black bottle containing a highly concentrated solution. Should any patient cry out or ask for a service, he was forced to take a drink from this bottle, whose salty-tasting contents stimulated thirst, which in turn was satisfied only by another swig, until the patient inevitably became drugged into a stupor in which he no longer bothered his attendants.

In the treatment of the psychoneuroses, sedation has long been used as an aid to psychotherapy. The drugs employed dulled the patients' awareness of their anxieties or decreased their physical symptoms and made them temporarily more susceptible to the influence of reassurance, suggestion and persuasion. By decreasing inner tension, they furthered diurnal rest and nocturnal sleep which were the cardinal objectives of the historically famous "rest cure." Differing only by quantitatively

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greater stupefying effects, the more recent continuous sleep therapy has been and is still being used for catatonic excitement, panic states and even acute war neuroses. These methods "cover up" the patient's anxieties and conflicts with the intent that his internal powers of control and capacities for recovery should be given the opportunity to function. As I shall indicate later, this concept has a limited validity but it indicates that even today sedation is often prescribed for the same reasons as in the past. The patient is quieted and does not bother his physician with complaints that he is incapable of understanding or treating.

In the modern practice of psychiatry the most experienced and skilled therapists use the least amount of sedation. They use it as an adjunctive method, with full knowledge of the pharmacological effect of various drugs on specific functions of the nervous system, to further the influence of dynamic psychotherapy. The technique of sedation has progressed from its role of making the patient quieter, easier to handle and less of a nuisance to the physician, to a sharp tool for the purpose of uncovering the patient's unconscious sources of anxiety and helping him master them.

## Pharmacology

Sedatives, hypnotics and anesthetics act on the central nervous system.[1] They enter into easily reversible combinations with the surface membranes of the nerve cells decreasing their capacity for oxygen utilization and hence depress their physiological activity. Minor variations in the chemical structure of the barbiturates alter the effective dose, the speed of action and the duration of effect. Various drugs act on different levels of the central nervous system, probably due to their specific affinity for cells of special chemical constitution (pathoclisis). Bromides and phenobarbital as well as dilantin are cortical depressants probably active on the internuncial neurones of the cortex producing a functional de-afferentation. Most of the barbiturates act first or more intensely on the diencephalon.

The best known sedatives are the bromides. These drugs have a much longer-lasting effect than the barbiturates which are rapidly excreted. Bromides replace the chlorides in the blood plasma and in the red blood cells in a chemical combination which takes time for its dissociation. The quantity of bromide that becomes fixed in the blood

depends on the chloride intake and excretion and the degree of hydration. As a result, the quantity of blood bromide may vary greatly in a patient who is on a constant bromide dosage. He may suddenly develop a bromide intoxication from a change in his chloride balance. Hence, bromides are uncertain drugs and require constant blood bromine determinations to avoid a dangerous quantity above 250 milligrams per cent.

Tatum and Seevers[2] proved by animal experimentation that long-continued administration of barbiturates produces severe disturbance of metabolism and ultimately death. My neuropathological studies of the brains of these experimental animals revealed profound morphological changes due to direct toxic influence of the drug. Suicides from overdoses of barbiturates have furnished sufficient neuropathological material to indicate that the human brain is likewise damaged by the long-continued use of this drug. Therefore, it becomes an important consideration for the physician not to facilitate addiction to sedatives. Habituation to sleep-producing medication is more in the nature of a psychological habit than an addiction. Abstinence from these drugs does not cause severe withdrawal symptoms so characteristic of the morphine addict, but does cause a marked accretion of anxiety and its physiological concomitants. In most states there are laws against the sale of barbiturates to the public without a doctor's prescription. It is the physician himself who is culpable, in most cases, by giving large quantities of the drug and assuring the patient that it will do no harm and is not habit-forming.

Actually, tolerance is established for the barbiturates and larger doses must eventually be prescribed. Those physicians who are content to use the drug as a covering-up technique find themselves not only prescribing increasing quantities but also shifting from one type to another until the wide range of barbiturates marketed under various trade names by a large number of pharmaceutical houses has been exhausted. To avoid this tendency to develop tolerance it is better to stop medication for a few days than to change the medication. Effectiveness of the drug is then rapidly restored.

In order to understand the action of sedatives with specific localized effects it becomes necessary to know something about the hierarchical structure of the central nervous system. This complicated structure has slowly evolved into its present complicated and adaptive functions by

developing new functional structures at its head end (encephalization). Sometimes these new functions are only more adaptive and complicated refinements of older, more primitive functions of lower centers, which they also inhibit.[3] Evolution is thus associated with a continuous increase of long-circuiting of external stimuli higher up the central nervous system. From a rapid and stereotyped simple and unconscious reflex activity of the spinal cord, behavior in man has evolved into a slower, especially adapted cortical function based on experience of past failures or successes.

The reverse of this process, known as devolution, occurs when one of the higher centers is affected by disease. Then the new function is obliterated, evidenced clinically by the loss of certain finer types of performance. But the majority of the symptomatology is of a positive nature in that the diseased center's loss of control over lower structures releases their activity, which may take the form of apparently new and certainly abnormal movements and behavior.

The same effect is achieved when a higher center is put out of control by a drug which paralyzes its function temporarily. A drug which sedates higher functions will produce the same loss of function and release of control over lower centers. Sedative drugs or anesthetics in increasing dosages may knock out the function of the entire nervous system from the cortex all the way down to the spinal cord, eventuating in complete paralysis and death. But by the quantities used in clinical practice two areas of the brain are most frequently affected, sometimes in sequence and sometimes selectively. These are the cerebral cortex and the diencephalon. It is well, therefore, to understand the phasic relationship between these structures.

The diencephalon includes the thalamus, the major nuclear body that receives all sensory impressions derived from outside and within the body. It sends fibers to the hypothalamus which is the diencephalic coördinating center for effector visceral responses. Through its stalk connections with the pituitary body it initiates a slow humoral, and, through its connections with the automatic nervous system, it effects a rapid change in homeostasis, adaptive as response to variations in the external environment. It effects those objective emergency responses which are the somatic correlates of anxiety. It not only sets into action autonomic responses but it also stimulates cortical activity. There is no diencephalic sleep center; to the contrary, it has a driving effect on the

cortex. The hypothalamus may be set into action not only by unconscious reflex processes but it may also be called upon by the cortex which perceives the dangerous meaning in the future from impressions received from the special senses. But in turn the cortex inhibits the hypothalamus from excessive responses. It is this phasic relationship which becomes of the utmost importance for our understanding of the use of sedatives in psychiatry.

Small quantities of anxiety in the form of a basic apprehension are economical to the organism, alerting it to external dangers. Larger quantities of anxiety and its physiological concomitants are pathological and displeasurable. They may arise from weakened control of hypothalamic activity by the normally inhibiting cortex, or from excessive or disturbed activity of the hypothalamus. Thirdly, cortical interpretations of external stimuli as dangerous, hence calling for emergency responses, may develop as conditioned reflexes which are no longer necessary and may be non-discriminating. To the neurotic more and more of the environment may seem dangerous and an excitation to anxiety and alerting reactions.

Sedation or depression of the cortical inhibiting structures releases increased activity of lower structures. As an example, ether gradually affects the neuraxis from the cortex down, producing an excitement release stage preceding generalized flaccidity. Alcohol is an irregularly descending depressant and only first acts on the cortex releasing previously inhibited behavior. In fact, the superego, or internal check on primitive asocial behavior, is facetiously defined as that part of the personality that is soluble in alcohol. Both alcohol and ether in small doses produce a state of facile expression and liberation of buried feelings and repressed thoughts, and have been used to effect abreactions. These, however, are relatively ineffective because in that stage of depression cortical activity is extinguished and learning is not possible. However, it is clear that sedative doses effective in reducing anxiety must be large enough and act fast enough to depress both the cortex and the hypothalamus simultaneously. The resulting sleep in exhausted patients may be followed by a resumption of normal cortical control of hypothalamic activity.

The barbiturates, for the most part, act on the hypothalamus, at least first, decreasing excessive autonomic activity. Alcoholic excitement caused by cortical depression is controlled therapeutically by intra-

venous injections of barbiturates. The same method reduces all psychomotor excitement in panic states or catatonia. By decreasing hypothalamic activity, that structure's bombardment of the cortex is reduced and permanent results may ensue from a breaking up of abnormal closed circles of internuncial neurones.

Finally, the destruction of abnormal conditioned reflexes may be effected by finely graded doses of sedatives which depress both cortex and hypothalamus less than the degree producing sleep. Then the driving force of the lower centers is reduced, cortical reactions to signals of danger are decreased and a new learning process may be endured, thus breaking up the no-longer-economical conditioned reflexes.

### Anxiety and Insomnia

Psychoneuroses are the result of conflicts between opposing inner psychological forces or between certain drives within man and his restricting, frustrating or punitive environment. At some time or other, such conflicts are signaled to the ego by the feeling of anxiety which is accompanied by physical symptoms manifested by altered functions of the visceral nervous system and by disorders of sleep. Both the subjective and objective components of this reaction differ little from those due to fear of a real external danger, in fact, man often projects the source of his unendurable free anxiety to an apparently rational environmental stimulus.

Anxiety, which is a signal felt by the ego of anticipated danger to its stability by threatened abandonment by external supporting figures, or disapproval by its own ego-ideal, or overwhelming force of its internal drives, is unbearable in free form beyond a minimal alerting quantity. Large quantities are either bound by somatic symptoms or projected to external rationalized fears. But in any case the patient comes to the psychiatrist pleading for relief of insomnia and his direct and indirect manifestations of anxiety. He wants immediate relief and cares not what the cause. In fact, he tried to run away from his symptom, literally and figuratively. Attributing it to a specific environment he will travel, leave his job or change his wife. He will deny its internal source, but refuses to adopt any procedure that will intensify his feelings.

What should the doctor do? Help him run away by manipulating his environment and decreasing his perceptions of anxiety by dosing him with sedatives, in other words, cover up the source of the anxiety, or

uncover the cause and help him master it?

According to our physiological concepts of the organization of the central nervous system, the task in anxiety is either to strengthen the anxiety-controlling mechanisms, the cerebral cortex, to decrease the pressure of the anxiety forces from the diencephalon, or, most logically, to liberate the anxiety in small doses and assist the patient in mastering it through a process of learning.

## Continuous Sedation

The continuous use of sedatives for the treatment of neuroses is employed not only by physicians who try to hide the symptoms and anxiety from themselves and their patients, but also by those who have a biologic and deterministic view of the neuroses. Sargant and Slater[4] state that symptomatic treatment is our only aim because we know so little about psychology. They believe that most psychological abnormalities are expressions of unknown constitutional derivatives not susceptible to direct attack. They recommend alcohol for psychopaths, feeling that it makes them lead a happier, more normal, better adapted life. They believe in the old James-Lange theory of emotions when they state "We feel fear with our bellies. Abolish this autonomic symptom and we abolish fear."

The majority of chronic anxiety states are little benefited by continuous sedation. Certain exceptions to this dictum include those who have acute flare-ups of anxiety bordering on panic states, or those whose anxieties are forcing them into disastrous motor action or abnormal behavior. In these cases it is often necessary to give large doses of barbiturates by mouth or intravenously, or paraldehyde.

In combat, many men succumb to overwhelming anxiety because their control has diminished by long exposure to cold and wet and long periods of strain without sleep or food. Their cortical control has weakened and a plateau of anxiety has displaced the normal sharp increment and slow fall in response to emergency situations. They are "too tired to sleep" by which is meant an excessive hypothalamic activity uncontrollable by the cortex. For these men, sleep induced by adequate sedation usually rehabilitates their control in a few days. After 5 to 7 days many are able to return to combat. Should anxiety persist beyond this point, processes have crystallized irreversibly which are not stopped by these simple procedures. The neurotic mechanism then requires

definitive psychiatric treatment.

Although, for conditions of exhaustion, cortical depressants seem to aid the anxiety-controlling mechanisms to regain strength, there is some evidence that these drugs may be harmful, delaying or preventing learning processes. Watson and Kennard[5] found that the cortical depressants phenobarbital and dilantin delayed the recovery of function following cerebral cortical lesions in experimental animals and neutralized the enhancing effect of Doryl, a cholinergic drug. The sedatives decreased the capacity for cerebral reorganization. It is common clinical experience that bromides and phenobarbital in analeptic doses depress attention and learning, especially in children. Thus continuous sedation, by interfering with the most efficient cortical functioning, may be harmful by decreasing the patient's spontaneous processes of learning and readjustment.

Patients with depression associated with considerable tension manifested by excessive psychomotor activity, usually characterized by pacing up and down, wringing of the hands, and generalized restlessness, may require, in the acute phase, day and night sedation. It has long been noted that barbiturates in themselves have a generally depressing effect on the mood. It is therefore unwise to give a depressed patient a drug which deepens his symptom. It is an old discovery that the only sedative that helps and does not deepen depression when given over a considerable period of time is opium. One-half to three-quarters grain of powdered opium in capsule form three times a day, in combination with sufficient quantity of a laxative such as Cascara to negate the constipating effect of the drug, is a standard symptomatic remedy for depression.

Some patients complain not of the free anxiety but of the stimulating effects of anxiety on both smooth and somatic musculature—producing spasms. Symptoms such as spasm of the colon may be helped by drugs like atropine which are sedative to the sympathetic activity. When anxiety is manifested by spasm of the voluntary musculature in the legs or back, relief may be obtained by the use of neostigmine or prostigmine. Just like hypnotics, these quieting effects are symptomatic rather than etiologic remedies.

There is a common mistake among many physicians that anodynes are good hypnotics. Even if the anxiety manifests itself by pain, such drugs as morphine should not be given. It has no place as an adjunctive for psychotherapy.

### Sedation for Insomnia

Patients with anxiety are anxious to get relief from their symptoms and little interested in their cause. They want immediate relief, particularly from the earliest and usually severest symptomatic evidence of anxiety, namely, insomnia. Patients whose anxiety is a signal of an aggressive trend which is rising to the surface usually have a bona fide desire for a sleep-producing drug. However, in them, relief from insomnia is seldom complete and they are usually disappointed in the results obtained from barbiturates.

Passive and dependent individuals whose anxiety is based on the frustration of their regressed needs desire medication of some sort as an indication that the physician is doing all that is possible to help them, and that he recognizes the medical disturbance. Failure to give medication is interpreted to mean the converse, that is, the denial of illness. The patient then feels that the doctor attributes his symptoms to imagination or malingering. It is as if he says "He's not doing anything for me because he thinks I'm putting on, or he doesn't care anything about me."

Although we realize that the source of anxiety has to be uncovered by work on the part of both the patient and the doctor, it is often necessary to convince the patient of his doctor's interest and understanding. The temporary use of a sedative may not only relieve the temporary insomnia but assist in furthering a positive relationship of the patient to his doctor, in other words, a transference relationship.

On the other hand, passive and dependent individuals may persist in requesting sedation even though their psychological state has progressed toward recovery beyond the stage at which such medication is needed. The request then becomes an attention-getting mechanism and the drug has a psychological effect. This impression is gained by the fact that satisfactorily disguised placebos administered under the guise of a sedative are not easily differentiated from the actual drug and seem to have the same effect. Thus it is the fact that a medicine is administered rather than its pharmacological effect that helps the patient gain his sleep.

Patients with severe anxiety usually have a very high tolerance for barbiturates, which may be due to the high level of nervous excitation which requires a larger dose to sedate. On the other hand, there is some evidence that acute anxiety states alter absorption from the stomach and intestinal tract which would therefore delay the effect of drugs adminis-

tered by mouth. As evidence for this phenomenon is the fact that many patients with anxiety have an excessively long "hangover" effect from the use of barbiturates which could be due to a slow absorption.

Self-medication for insomnia in the form of alcohol is quickly adopted by many patients with acute anxiety, and there is no question that in small doses alcohol's depressing effect on the cortex decreases the impact of the anxiety-producing mechanisms. But, unfortunately, alcohol is rarely imbibed in pharmacological doses, and quantities greater than the optimum effect are usually ingested. Many "shell-shocked" veterans of the last war have learned that comfort may be obtained by the use of ½ grain of phenobarbital in combination with a few bottles of beer. Both the drug and the alcohol are cortical depressants. However, when the alcohol or the phenobarbital has depressed the cortex so much that it not only does not permit the apperception of anxiety stimulated from activity of the lower centers, but also loses its inhibitory effect, anxiety and its effects become accentuated. During this phase they very frequently act out extremely violent abreactions and often become extremely aggressive and perform asocial and often criminal acts. For these people a sedative which acts on the hypothalamus is necessary to reduce the effect of the anxiety-producing mechanism since there is no longer any cortical control of it. Large doses of paraldehyde, or better still, intravenous sodium amytal, are usually necessary to sedate such people.

The anxiety-ridden patient not only has difficulty in getting to sleep but he has trouble maintaining this state for any length of time. The most effective use of barbiturates consists of a combination of a quick-acting and a prolonged-acting drug. For this reason, combinations of seconal and nembutal or amytal or barbital are advisable.[6]

Sedatives that are temporarily given to patients should be accompanied by pertinent instructions as to the meaning of both wakefulness and the sedation. They should be told that sedatives are temporary corrections and that wakefulness is but one aspect of their illness which can only be helped by an understanding of its meaning in terms of past experiences. They are easily led to understand the futility of large covering-up doses by reminding them that acute anxiety breaks through and destroys sleep by bringing up old unmastered memories.

It is a strange habit of pharmacopeias and compendia of remedies to indicate minimal and usually ineffective doses. Not only are sedatives

of no value in small doses but they are also harmful. A few examples may be given; 1½ grains Seconal, in an acute anxiety, is usually ineffective, hence its dose should be doubled. Nembutal is better given in doses of 3 gr. and sodium amytal 3 to 6 gr. Four or five drams of paraldehyde by mouth and 10 cc. of the same drug intramuscularly is most effective. There is no standard dose of sodium amytal by vein. It should be given regardless of the dosage until the physical effect is obtained. Medication has no purpose unless it is given in effective doses. When accidental or self-administered overdoses of barbiturates produce dangerous coma, intravenous picrotoxin or metrazol are good antidotes and should be used in dosages sufficient to arouse the patient.

## Continuous Sleep

Continuous sleep is a procedure first developed abroad and then applied in this country to a varied group of agitated psychotics and neurotics with panic. At first it seemed to have some success in the excited catatonics, but gradually enthusiasm for this therapy has diminished. Nevertheless, it was applied to the treatment of acute war neuroses associated with much anxiety. Spiegel and I found it ineffective in reducing anxiety or furthering psychotherapy.[7] Hastings, Wright and Glueck[8] reported excellent results but re-evaluation of their work by later psychiatrists in the same Air Force did not substantiate this enthusiasm. However, even yet certain military psychiatrists use modified continuous sleep and sub-shock doses of insulin. We repeated the continuous sleep treatment on anxious returnees and found that not only was it therapeutically ineffective but it also made the patients worse. Our first 20 patients were all medically discharged from the Army.

I shall not give the details of the technique except to state that 4 out of each 24 hours must be waking hours for the purpose of physical movement, toilet function and feeding. During the rise into awakeness and the sinking into sleep, twice daily, the borderland state is associated with terrifying hypnagogic hallucinations and panic-inducing anxiety. Lasting so long and experienced without the support of the therapist, such episodes seriously weaken the anxiety-controlling mechanisms still further. The uncontrolled delirium becomes destructive.

The human organism frequently adopts a technique reminiscent of the instinctual defensive immobilization of lower animals. Confronted

by external danger, the rabbit or the guinea-pig may not fight or run away but may merge itself, immobile, with the protective coloration of its environment. Men with war neuroses frequently shut out all sounds, sights and memories of the dangerous events by retreating from the anxiety-stimulating conflicts into stupor, deafness, muteness or blindness. In certain civilian neuroses we frequently find that instead of free anxiety and insomnia the patient adopts the defense of hypersomnia and sleeps for much of the day and night. Just like the stupors in combat, such defenses are uneconomical and unadaptive. They should not be imitated by an active therapeutic principle of inducing continuous sleep.

### Uncovering Techniques

Aside from their use to produce continuous sleep and for sedation in states of exhaustion, barbiturates are used in psychiatry for the purpose of facilitating uncovering techniques of treatment. Although the doses utilized are non-toxic and devoid of danger, the psychological effects are not without harm if the procedures are carried out by unskilled physicians who have not been adequately trained in dynamic psychiatry. The quantity of liberated emotion may overpower the patient's weakened anxiety-controlling mechanisms unless the therapist is skilled in assaying the patient's capacities to synthesize and integrate feelings that have been repressed and which will be released under the treatment. Nevertheless, in skilled hands intravenous barbiturates considerably shorten individual psychotherapy when used as a part of the treatment.

Treatment techniques of the uncovering type are especially utilized in neuroses for the purpose of ventilating repressed feelings and ideas which are etiological to the nervous symptoms. Such uncovering during individual psychotherapy is but the first step in the work of mastery of reactions initiated by external stress. Shortacting intravenous barbiturates hasten this process by quickly overcoming resistances, by decreasing the pain felt by the ego in the process of recall and by effecting a release of feelings in small doses.

Repressed painful or traumatic events and the repressed anxieties and hostilities connected with them are not only exposed during the treatment, but accepted by the patient's ego. He then is able to deal with them in a more economical and realistic fashion, giving up the neurotic compromises which have resulted in his symptoms. This is the process

which is called *narcosynthesis,* since under the action of the drug and with the aid of the therapist, the previously repressed or forgotten feelings and memories are synthesized by the ego. If this process has taken place, the degree of recovery will then depend upon the new grouping of forces within the ego.

*Diagnosis* is furthered by the drug enabling the observer to gain a clear view of the intensity of anxiety, the degree of regression, the strength of dependent trends, the superego attitudes and the dynamic relation of all these factors to each other. The knowledge thus gained can be of great advantage to the psychiatrist in relation to further treatment, even in the absence of any clinical gain to the patient. The repressed emotional situation may be clearly exposed and abreacted in the narcotic state without its achieving any synthesis. Since the material in this event is lost when the individual arouses from the effects of the drug and no change has occurred in the relative strengths of the dynamic forces, there is no symptomatic improvement. This is not infrequently the case in patients whose resistances are very strong, or those whose ego depletion is severe. It is also seen in individuals with rigid super-egos in whom there is strong guilt over real or imaginary failure to live up to ego ideals. In the latter case the failure of synthesis as well as the persistence of severe symptoms appears to be related to an unconscious dynamic need for self-punishment. In this context, the treatment is identical with the *narcoanalysis,* long used in psychiatry, in which the benefit results almost entirely from the insight the therapist gains concerning the patient's concealed difficulties. In a similar manner the method may be utilized for diagnostic purposes to determine the progress a patient has made after therapy.

As a means of inducing *narcohypnosis* intravenous barbiturates are successful, but the effect of persuading or forcing the patient to give up his symptoms by strong suggestion is not long-lasting since the basic causes are not exposed. This procedure is not recommended except for purposes of expediency.

The method should not be used in debilitated individuals suffering from cardiac, renal, hepatic or pulmonary disease. It should not be used during the time that the patient has an upper respiratory infection. These drugs are ineffective following prolonged alcoholism so that drinking should be interdicted at least 24 hours before the treatment.

Schizophrenics and manic depressive psychoses that are highly endog-

enous should not be treated by the method because of the danger of precipitating an overt psychosis or making an existing psychotic state worse, and the danger of precipitating suicidal actions. Patients in a near panic with severely weakened egos, especially those suffering from homosexual conflicts close to consciousness, may be worsened by rapid uncovering techniques. Patients with long-standing character neuroses and psychoneuroses existing prior to stress, psychopathic personalities and compulsive-obsessional neuroses and characters are usually not benefited. The method cannot lift the amnesias produced by alcoholism or cerebral concussion.

Favorable cases are young and plastic individuals who have developed neurotic symptoms as a result of external stress and whose predisposition has been mild or minimal, and patients with repressed conflicts producing regressed dependency reactions, depressions, guilt, hostile aggressive reactions and psychosomatic syndromes of recent origin.

For some individuals who are frightened of the treatment, of receiving an injection, or the "needle," or of the deleterious effects of a drug, further reassurances may be necessary. However, once explanations are attempted in order to reassure an apprehensive individual, further questions are stimulated which require further explanations, so that one must be prepared either to say very little about the treatment or else to give a lengthy dissertation on the subject.

In general, it is wisest not to initiate the treatment until some degree of confidence has been established in the therapeutic relationship and some transference attitudes have developed, although this is not always possible or necessary. Hence, the treatment should never be given until one or more psychotherapeutic interviews have been given and the therapist is familiar with his patient's background, his stress and reactions. If the treatments have been in progress in a hospital or some other institution, the easily observed clinical benefits and the lack of harmful or unpleasant reactions will have produced a general acceptance of the procedure, and individual resistance to it will be minimal.

Sodium amytal or sodium pentothal may be used as desired. The latter has the advantage of being quicker acting and shorter lasting, thus enabling the patient to be entirely conscious at termination of the interview and able to return to his ward alone.

The nurse's tray should contain, in addition to the drug, ampoules

of metrazol and nikethamide (coramine) and an airway in case of choking, coughing or cyanosis indicative of edema of the glottis. Fortunately, this hardly ever occurs in the dosage necessary. Apnea, which may occur transiently for a few moments, is almost never sufficiently prolonged to require therapy.

Sodium pentothal is issued in ampoules of 0.5 gram and 1.0 gram and may be administered in either a 2.5 per cent or a 5 per cent solution. The dosage required for a satisfactory narcosis is usually between 0.25 gram and 0.5 gram, though in some very marked anxiety states in large individuals, more than 1.0 gram may be necessary. The individual reclines upon a bed in a semi-darkened room and is told that he is going to receive an injection which will make him sleepy.

The drug is injected into the antecubital vein at a slow rate (0.1 gram per minute), while the patient is asked to count backwards from the number 100. Shortly after the counting becomes confused and before actual sleep is produced, the injection is discontinued, although the needle may be allowed to remain in the vein until it is ascertained that the proper depth of narcosis has been achieved. This may be deceiving. Some individuals suddenly fall asleep in the midst of their counting, only to become wide awake and alert on slight stimulation. In such cases, more of the drug must be injected. If the individual is mute or stuporous and therefore cannot count, a corresponding depth of narcosis must be estimated from the tonus of the eyelids and pupillary reflexes. In rare instances, the injection is difficult because of a violent tremor of the arm. In almost every case, there is some increase in the symptoms of anxiety as the injection is initiated. As it proceeds, however, the tremors subside and the individual becomes quiet. Speech may be somewhat thick and there may be spasmodic coughing but serious pulmonary difficulties with the doses and technique described are rare. Vomiting during or after the injection is rarely seen.

By the time a satisfactory level of narcosis is reached, a few individuals will begin to talk spontaneously. In the greater number of cases, verbal stimulation is necessary. The amount of stimulation which must be given in order to start the individual talking and to bring him into contact with his painful experiences varies tremendously. Some react with the first few words, selecting a crucial stimulus and launch into an account of the experience. Others resist for various periods of time. When such resistance is maintained, the stimulation can be made more

dramatic and realistic.

The individual reactions during the progress of the treatment are extremely varied. In some men the situation is relived with such intensity that the activity requires a motor rather than a purely verbal outlet. Others live through the scene verbally and emotionally without much motor activity. The tendency to live through the various combat episodes in the present tense leaves large gaps in what the therapist can grasp of the action, like listening to one end of a telephone conversation. The patient, therefore, is constantly urged to recount the episodes in the past tense, giving a clear picture of what took place. The minuteness and wealth of detail which floods the memory, even for events which took place many months and even years past, is always impressive.

The events which are depicted with the realistic impact of an expert dramatic production are probably always true counterparts of what actually took place, rather than fantasies such as are produced in dreams or hypnotic states. The emotional reactions, however, do not represent necessarily the actual behavior during the original episode, but rather what the patient repressed and controlled in order to carry on.

Some men return over and over again to one short traumatic scene, living it through repeatedly. In such cases, more than one pentothal treatment may be required, each one bringing out new pieces of repressed material as if the ego's tolerance for the painful memories increased in the intervals between each treatment.

During the time that the patient is in a close emotional contact with the traumatic situation, the therapist may play an active or passive role in the performance to the degree required by the process of the abreaction. No attempt should be made to produce an hypnotic situation, nor to direct the material into any definite channels unless there is a clear indication that resistance has developed to the communication of some thought, event, or feeling which was on the point of emerging. In this case, the therapist may encourage or exhort the patient to communicate the painful material. In most instances, if the resistance is still powerful under the influence of the drug, no amount of work on the part of the therapist will be of much avail, although another pentothal treatment at a later time may accomplish the desired result.

The therapist usually remains as a vague background figure, from which vantage point he can step into other roles as it becomes necessary. Many men, especially those with free anxiety, a stable ego organization

and a firm contact with reality, are aware of the psychiatrist's presence throughout the treatment. They talk to him directly, telling their story in the past tense and relying on him only for moderate support and sympathy during moments of strong emotion. Others, in whom there has been more dissociation of feeling and who "live through" their experiences under pentothal with great intensity, need more active support.

The therapist may be called upon to play a variety of roles. If the patient becomes convulsed and blocked with the violence of fear, he must step in as a protective and supporting figure, comforting and reassuring him. When intense grief and anger or guilt are exhibited, a forgiving and supporting attitude is required. At the same time, some steps may be taken here to point out the irrationality of the guilt, although this is usually best left to a later point in the session when the individual is no longer under such strong emotional stimulation.

Some men who talk constantly throughout the session to their friends become blocked at certain points either because of the intensity of the emotion or because they seem to get no response from their friends. The therapist may then play the part of the friend, stepping into the scene in an active role.

The manner in which the therapist handles the abreaction is an index of his psychodynamic knowledge. He must avoid the liberation of quantities of anxiety which will overpower the ego, yet permit sufficient ventilation. He should permit free associations, not interrupting with questions based on his preconceived notion of the repressed material. He must interpret the productions of the patient and not expect them to be entirely and directly revealing.

As the effects of the drug wear off and the depth of narcosis decreases, the patient enters that twilight area in which he is still strongly in contact with painful situations and the feelings aroused by them, and yet is increasingly in contact with his immediate environment, the therapist and the present reality. It is at this point that the therapist begins to play an increasingly active role. His immediate concern is to make sure that the material which has just been abreacted is actually synthesized into consciousness. Because of the short-acting effect of sodium pentothal and the absence of the prolonged period of sleep seen with other drugs, the circumstances are mechanically favorable. Still, in some instances where the resistances are too strong, a synthesis cannot

be established. In such circumstances, the individual usually snaps out of the narcosis into an alert or partially confused state, but completely amnesic for what he has just been saying. A review of the material may bring it back into memory, in whole or in part. On the other hand, efforts to effect a recall may fail and the individual remain completely blank for the entire experience. Pentothal productions should not be read or played back to the patients. The process of remembering is an important work of the ego. The patient should be seen again the next day or as soon thereafter as possible.

In the majority of instances the transition is smooth and the material is spontaneously synthesized into consciousness. Then, because the dynamic forces at work are at the moment so labile and freshly stirred up, the therapist has an ideal opportunity to effect a modification by active interference. Superego attitudes can be easily influenced at this time in the direction of effecting new identifications.

In those with conversion symptoms or protective phobic reactions in whom the ego has for the first time faced the full intensity of the actual anxiety, the symptoms spontaneously disappear since they have lost their functional purpose. However, the ego is in need of encouragement and support for its new frankness. Although in losing the protection of the symptom the ego must suffer the pain of free anxiety, actually in many instances considerable gratitude and relief is expressed as the individual finds that he can do this without suffering too much or losing too much prestige.

During the abreaction, the pharmacological effect of the drug plus the presence of the therapist has enabled the ego to face the painful situation and express its anxiety. The very act of abreaction reduces the pressure upon the ego so that it can continue frankly to face the painful situation after the effects of the drug have worn off. With the pressure relieved, and aided by the therapist, the ego finds that it is stronger than it had anticipated. For the vicious circle which had perpetuated the neurotic compromise in which the ego was continually weak and incompetent, a "benign" circle is substituted. The ego can afford to look squarely at the situation which it had been unable to master and therefore avoided, in part, at least, and to find a new strength. It is encouraged to find new and more efficient techniques to master the situation or at any rate to control its anxiety.

Pentothal is never the entire treatment but must be followed by

individual psychotherapy and group psychotherapy or group therapy, depending on the available time and personnel. The ventilated material must be synthesized by "working through."

The capacity of the ego to synthesize the material released from repression is not dependent on the patient's ability to verbalize insight or to repeat the material in a conscious state. Progress of the total therapy should therefore be judged on the patient's symptoms, attitudes, feelings and behavior and not on his intellectualization.

## Summary

Sedation as a technique in psychotherapy is not a simple matter of prescribing a standard dosage of an advertised drug. It requires an adequate understanding of the pharmacology of the sedative, of neurophysiology and of psychodynamics. Sedation is adjunctive therapy and has an important place in its proper role in the total program of treatment. It may help the organism increase its control over anxiety; it may reduce the quantity of the force of anxiety and it may facilitate uncovering processes and subsequent mastery and learning. Sedation should always be employed in a scientific manner for a specific therapeutic purpose and never as a means of quieting the patient and thus making him less disturbing to his doctor.

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# INFECTIOUS HEPATITIS*

JOHN R. PAUL

Professor of Preventive Medicine, Yale University School of Medicine

INFECTIOUS HEPATITIS has a special interest for us today because it may well come to be designated as one of *the* diseases of World War II, in somewhat the same manner as pandemic influenza became one of *the* diseases of World War I. Both influenza and epidemic jaundice have been known for centuries, but it would be an understatement to say that they were the source of much *new* and unexpected trouble in World Wars I, and II, respectively. The story is also worth reviewing because it now seems so strange that a disease so common in many parts of the world and so important, should have remained so poorly defined and so poorly understood for so long—particularly in this country. The picture is still not perfectly clear, but the fact emerges now that infectious hepatitis has been masquerading under a variety of names of which at least four can be listed as:— 1) catarrhal jaundice; 2) acute yellow atrophy of the liver; 3) Weil's disease, and 4) serum jaundice.

Before attempting to say how much or how little of these four conditions are actually included under the term infectious hepatitis, it may be wise to give a brief clinical picture of this disease so that it may be clearer what we are discussing. Primarily the term *infectious hepatitis* refers here to the same disease which the British call *infective hepatitis*, and others call *epidemic jaundice*. As the name indicates it is an infectious disease. It appears either sporadically or in large or small epidemics. Family outbreaks are traditional with the disease appearing first in one member and then about a month later, in other members. Early symptoms point to a disturbance in the upper gastrointestinal tract; evi-

* For much of the material used in this lecture I am indebted to Major W. P. Havens, Jr., M.C., Director of the Hepatitis Laboratory of the *Neurotropic Virus Disease Commission, U. S. Army Epidemiological Board,* Preventive Medicine Service, Office of The Surgeon General, and to other members of the *Hepatitis Study Group* also of the above Board. Information has also been obtained from the reports compiled by Col. M. H. Barker, M.C., and his colleagues in the North African and Mediterranean Theatres of Operations of the U. S. Army in 1942-1945.

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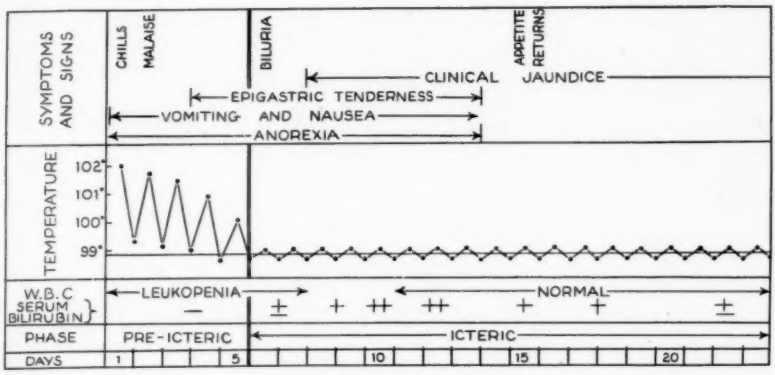


**Fig. 1. Schematic diagram illustrating the clinical course of an average case of infectious hepatitis in an adult.**

dences of liver damage occur later. Clinically the picture is similar to that of catarrhal jaundice with a rather sharp division into two phases, *pre-icteric* and *icteric*, see Fig. 1. These two phases have characteristic symptoms and signs. The *pre-icteric* stage, which may last from five to ten days, is usually marked by anorexia, nausea, fever, and abdominal distress. The white blood count often shows a leukopenia to be followed by an increase in abnormal lymphocytes, and in this and other respects infectious hepatitis has certain features in common with infectious mononucleosis. The liver is seldom large in this stage but there may be splenic and cervical lymph gland enlargement. The *icteric* stage, which follows, may last from two to ten weeks. Jaundice is usual, but in spite of the name, clinical jaundice is not an essential part of the picture; milder cases do not show it. Usual symptoms in the *icteric* stage consist of abdominal discomfort, in the form of epigastric or right upper quadrant pain, continued nausea, enlargement and tenderness of the liver, and light or even clay colored stools. Before improvement starts there is apt to be a good deal of weight loss. The white blood count is normal in this stage.

The prognosis is good, for the disease is seldom fatal—about 2 per 1000 in adults. In many of those cases which are fatal, extensive and diffuse destruction of the liver is found—the picture of acute yellow atrophy of the liver. Fig. 2.

But it is not my purpose to give a text-book picture of this disease

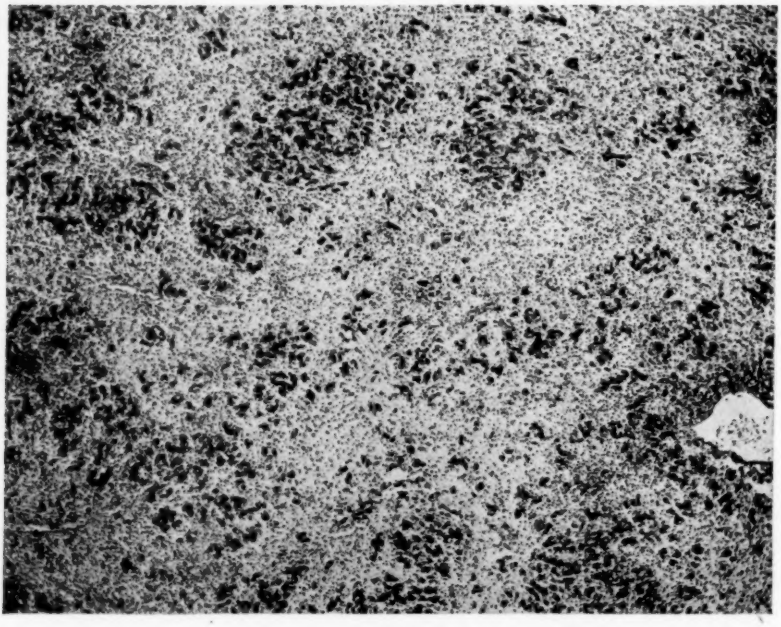

**Fig. 2. Photomicrograph (low power) of the liver from a fatal case of infectious hepatitis in which death occurred on the 9th day of disease. Great destruction of parenchymal cells is evident. Grossly the picture was that of acute yellow atrophy.**
**(From the Neurotropic Virus Disease Commission, Army Epidemiological Board)**

in this lecture.* Instead I propose to review its history up to the onset of World War II, and then to pick it up again after this point; for it would seem that that almost as much history has been written about infectious hepatitis since 1940, as was done in the entire preceding era. Certainly the war has been responsible for much of the recent impetus given to the investigation of this disease.

In my *historical* review I will pick up the threads from various sources and will draw heavily on the work of Cockayne, a British physician who published a review in 1912,[3] under the provocative title, "Catarrhal Jaundice, Epidemic Jaundice and its Relation to Acute Yellow Atrophy of the Liver." That the three conditions mentioned in his title may under certain circumstances represent one and the same disease is also the central theme of this talk.

* For further and more detailed descriptions of infectious hepatitis the reader is referred to articles by Havens;[1] or by Barker *et al.*[2]

Of this triad, catarrhal jaundice has the oldest history. It appears to have been well known to Greek and Roman writers. It attained the dignity of a clinical entity early, and is still regarded by some as a "respectable" disease. Its main attributes were that it was sporadic in distribution, and probably non-contagious. Its clinical course lasted from 3 to 6 weeks, and it was non-fatal. If these laws were broken the tendency was to change the name, *i.e.*, if multiple cases occurred, catarrhal jaundice became epidemic jaundice; if the clinical course was a short one, it might be called bilious influenza, or if long, bilious typhoid; or if fatal, it became toxic hepatitis or acute yellow atrophy of the liver.

The pathology of catarrhal jaundice has been based correctly enough on the concept of duodenitis as the primary lesion. But there also was a conviction that, as the name rather suggests, the jaundice was obstructive and due to a "plug of mucus" to be found in the common duct at the ampulla of Vater.* First hand accounts of this plug are few because patients seldom die with the diagnosis of catarrhal jaundice and the pathologist was fortunate indeed to have the privilege of examining at necropsy a fatal case of this disease.

The master pathologist, Virchow, had seen such a case in 1865, with a mucous plug in the terminal portion of the common bile duct. A few others have reported similar observations and this has convinced some in the belief: "that cases of true catarrhal jaundice may occur either as a result of a primary ascending cholangitis or following inflammatory changes in structures such as the pancreas and lymph nodes in close relation to the bile ducts."[4]

An opposite view of catarrhal jaundice has long been held by many supporters who believed the jaundice to be due to a hepatitis following systemic infection rather than to the plugging of the bile ducts. According to Rich,[5] in the records of the 11,500 autopsies performed at the Johns Hopkins Hospital during 40 years, there is not a single case in which the diagnosis of catarrhal jaundice could be regarded as accurate. He says, "whatever may be the exact pathogenesis of this condition (which, indeed, probably represents a *mélange* of types of benign icterus of different etiologies), the clinical laboratory findings are unmistakably those of regurgitation jaundice"—as opposed to retention jaundice. So actually the general classification of catarrhal jaundice becomes essentially a clinical concept of unknown etiology, and some-

* For a discussion of literature dealing with historical aspects of catarrhal jaundice and infectious hepatitis the reader is also referred to the article by Findlay, MacCallum and Murgatroyd.[4]

what unsatisfactory pathology as far as the liver is concerned.

Another disease in Cockayne's triad was *acute yellow atrophy of the liver*. This has a long history too, supposedly going back to Ballonius, that early French physician who is also credited with the first description of rheumatic fever. The cumbersome term, acute yellow atrophy, to which the adjective *idiopathic* should also be added, fails to indicate much as to the nature of the disease or its etiology and there the situation has remained for many years. Admittedly an anatomical term, it is loosely given to those cases in which some unknown agent suddenly produces widespread destruction of liver cells. It is again a mixture of types of liver injury due to a variety of causes including "catarrhal jaundice," infectious hepatitis and chemical poisoning as well.

But we come to a more definite group of diseases when we begin to examine *infectious hepatitis*, or *epidemic jaundice* or *icterus epidemicus*. The earliest records of this group may also go back to Hippocrates but undoubted reference was made much later and comes from Europe in the mid 18th century.[3] From that time forward many outbreaks are recorded. The disease has a particularly long military history[6] for it was an old and ugly camp follower. It was common in America among the Federal troops in the Civil War. It has been common in many subsequent wars, notably World War I.

By the late 19th century it became apparent that there were at least two varieties of epidemic jaundice—the mild and the severe. The severe form was differentiated by Weil in Germany in 1886,[7] who described the disease which goes under his name. It can be readily differentiated from infectious hepatitis, as a serious infection with a high mortality. The rat has been incriminated as an important vector in its spread. The discovery of its spirochaetal etiology by Japanese workers,[8] in 1914 seemed to fascinate students of epidemic jaundice at that time. It may have so transfixed Dr. Noguchi that he announced shortly his belief that yellow fever was due to a leptospira. In any event the influence of this discovery was such that the term *infectious hepatitis* became for the time being synonymous with Weil's disease, and for a period of about 25 years most of the important American text-books (during the 1920's and '30's) eliminated from their lists the term infectious hepatitis as the name of a disease *per se*, embracing it instead under the title of Weil's disease. Perhaps this confusion may be attributed in part to the fact that there are erroneous reports during this period of finding the

spirochete *(Leptospira icterohaemorrhagiae)* in the *blood* in clinical cases. Today we realize that many laboratory workers have been led astray by the finding of artifacts in the blood, which bear an uncanny resemblance to a living spirochete.[9] A differentiation between Weil's disease and infectious hepatitis is important because of the discrepancy in prevalence between these two types of liver diseases. To date in the State of Connecticut, for instance, Weil's disease is a great rarity,[10] whereas hundreds of cases of infectious hepatitis may be seen in a single winter. Differentiating features are that there is a leukocytosis in Weil's disease while in infectious hepatitis the blood count tends to remain unchanged, except in the early period when there is a leukopenia. Furthermore the diagnosis in Weil's disease may be established in the early stage by guinea pig inoculation, and in convalescence by appropriate serological tests.

Still another development which tended, perhaps, to confuse the picture of infectious hepatitis during World War I and for a short time thereafter was, that as early as 1864 it had been described as the bilious form of typhoid fever *(typhus biliosus);*—and again as the bilious form of influenza, suggesting a *state of jaundice* rather than a clinical entity. The linkage to typhoid or paratyphoid fever and dysentery came from the fact that epidemic jaundice often occurred under conditions in which enteric infections were prevalent. This notion was strengthened during the World War I campaign in the Dardanelles in 1916, when French medical officers observed a military epidemic of typhoid fever turn into an epidemic of jaundice; in fact become, the "bilious form of typhoid."[11] Bacteria of the paratyphoid group were detected in the blood of these jaundiced patients in this epidemic as were also their specific antibodies. It was suggested at that time that such atypical strains of the paratyphoid group or salmonella (usually *Sal. schottmuelleri*) had acquired *new* characteristics, taking on an "icterogenic capacity." These findings were eventually discounted but they should not be forgotten. They have in fact, been justified in the new light of an important discovery in which salmonellae were recently isolated from the blood stream in two human experimental cases of hepatitis induced by the virus.[12] The men who volunteered for this experiment lived in an institution where salmonellosis was frequent. The bacteremia in these cases has been regarded therefore as an example of *secondary* infection. As such, the etiologic aspect of these salmonellae may perhaps be viewed in the same light as we

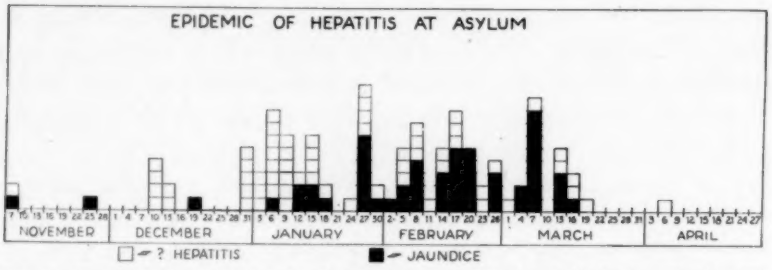


**Fig. 3. An institutional outbreak of infectious hepatitis in which both patients with clinical jaundice and questionable hepatitis (without clinical jaundice) have been charted. Each square represents one case.** (From Havens and Paul[40])

might view influenza bacilli in a case of influenza A or B.

A linkage with influenza is also understandable today. There are many cases of infectious hepatitis in which jaundice never becomes apparent. They may even be so common in some epidemics that the ratio of icteric to non-icteric cases may reach 1:1 or even more. See Fig. 3. The symptoms of these non-icteric cases are not very definite but include fever, malaise, and vomiting. Such cases might have been easily confused with influenza, particularly if the loose term of "intestinal grippe" is employed. When they are frequent in any particular outbreak it is not hard to see how the concept of the bilious form of influenza could become popular.[13]

This then was the rather confused state in which infectious hepatitis was viewed during the 1920's. Blumer[14] was among the first in this country in that period to uphold the identity of infectious hepatitis and to point out that it was common. He believed catarrhal jaundice to be the sporadic form of infectious hepatitis. Only recently have these views been widely accepted, and substantiated by a growing number of reports from England,[15] Europe[16] and this country, notably by Molner and Meyer in Detroit.[17] The latter described large epidemics of jaundice, obviously *not* due to the spirochete of Weil's disease. Proof of this lay in the fact that *serological* tests for Weil's disease had by that time come into being, and negative serological reports had been found in a great majority of their cases of infectious hepatitis, some of which prior to the use of this diagnostic test, might have been classified as Weil's disease.

This brings us to World War II—a landmark in the history of infectious hepatitis. Our first contact in this second chapter began shortly after the United States had entered the war; when the U. S. Army was

suddenly confronted, early in 1942, with a large outbreak of jaundice of unknown type. This new variety of jaundice did not remain unidentified for long, however, but was soon recognized as *homologous serum jaundice*,[18] described by Findlay and MacCallum[19] in 1937, and others[20] later but still relatively unfamiliar in 1942. Serum jaundice is an artificial disease readily spread as the result of transfer of the causative virus from one individual to another when infective blood happens to be drawn for use in transfusions, or as immune sera, or as in this instance, as a stabilizing agent for the preservation of yellow fever vaccine. This virus is similar but not identical to that of infectious hepatitis and the same might be said of the clinical picture. The two diseases appear to be cousins. It is also likely that some examples of "serum jaundice" actually represent the artificial transmission of infectious hepatitis, although one cannot say that all serum jaundice belongs in this category. The agents of both diseases besides being filterable are both resistant to heat at 56°C, both fail to infect any known laboratory animals and yet both give rise to jaundice in humans when inoculated parenterally. But in *infectious jaundice* there is usually a relatively short (25 days) incubation period, and in *serum jaundice* it is longer—60 to 150 days or more. An attack of serum jaundice does not produce immunity against infectious hepatitis. Moreover, there is another difference between the two, experimentally at least, in that an attempt to recover virus mid-way through the short incubation period of a subject experimentally infected with infectious hepatitis was unsuccessful—whereas during the much longer incubation period of serum jaundice, virus is apparently circulating in the blood for weeks. In one instance it was found 60 days prior to the onset of jaundice.[21] This means that in apparently healthy individuals there are long periods in which the blood is infective. These pre-illness carriers are of some danger to the community if they happen to be donors of blood or if they happen to be attending a clinic where immunization procedures are being casually used. The patient with active infectious hepatitis is not so dangerous, because of the fact that he is apt to be sick during his infective period and his symptoms alone would be enough to warn any physician not to use his blood for the various purposes for which blood is used today. The importance of this rests on the fact that numerous examples of serum jaundice have resulted from transfusions, from the prophylactic injection of serum for measles, for mumps, and other virus diseases, and apparently from the use of im-

properly sterilized syringes.[22] Serum jaundice therefore may be a variant form of infectious hepatitis about which we have learned by the hard way. But unfortunate as this experience may have been, it helped pave the way to the concept of using man as an experimental animal in a disease in which no laboratory animal was available. The use of human volunteers has in fact greatly increased knowledge of both serum jaundice and infectious hepatitis during recent years.

This brings us back to infectious hepatitis, to 1940, and the recent war. And it brings us back to the real problem with infectious hepatitis in this war, which was its unexpected prevalence in certain military zones. The disease was and is common enough in Europe and elsewhere, but it was in the Mediterranean area that its full import as a military disease was first encountered. Here in 1941, and the three subsequent winters there were many thousands of cases in British[23] and American[24, 25] troops. There is no good reason to believe that this disease was different from that seen elsewhere but it seemed to flourish better in the Middle East and the Mediterranean littoral, as it had in 1916. The disease was thought at that time (1940-43) to be spread by droplet infection although this view was not universally accepted. Actually this question of the mode of spread was of fundamental military importance, needing settlement at the earliest opportunity; for knowledge of the mode of spread of infectious hepatitis is the basis on which the whole program of prevention sometimes hinges.

It was in this part of the world, namely Egypt,[1] North Africa,[24] Sicily and Italy[2] where the disease was particularly prevalent among American troops. And it was also there that some of the investigative work on infectious hepatitis was started. For these investigations preliminary information derived from British military experience in the Middle East was invaluable to us. The work of van Rooyen and Gordon,[26] and Cameron[27] was particularly helpful. It is a tribute also to the Medical Department of the American Army in general and the Preventive Medicine Service in the Surgeon General's Office in particular, that they had the foresight to assign small teams of research workers to survey this problem in the field. It is fortunate also that the Medical Department in the North African and Mediterranean Theatres of operations in 1943-45 was able to assign a number of very capable medical officers to this problem in Italy, and some of their reports[2, 25] are now available to us. And finally it is appropriate to mention the part played

by many volunteers who offered themselves as subjects for these studies.

As a result of these Army investigations, the following facts some of them new, and others old but better clarified, were established. The disease has been repeatedly reproduced in humans by the injection or the feeding of the etiologic agent–now considered a virus. This virus has not been "isolated" in the sense that it has been seen or cultured or transmitted to laboratory animals, for repeated attempts in rodents and all sorts of monkeys and even chimpanzees[28] have been negative. But many of its properties have been established by using man as the experimental animal. It can be passed, for instance, serially in man.[29] It is filterable and it is quite resistant, withstanding heat at 56° c for one half hour,[29] as well as chlorination viz. one part chlorine residual per million –Neefe, *et al.*[30] It has been presumably found in drinking water.[31]

Among original claims of success at human transmission are those of Voegt in Germany, published in 1942.[32] Details are incomplete but Voegt described having infected a few volunteers by feeding them duodenal fluid, urine and blood. British studies were carried out in Palestine by Cameron[27] a year later when serum and whole blood from cases of hepatitis were injected intramuscularly into six British soldiers. A number of cases of jaundice were produced after an irregular incubation period.

A year later experiments were reported in England in a short note by MacCallum and Bradley[33] who found the virus in feces and found that the disease could be induced in arthritics who volunteered for these experiments by feeding this material. These results were independently duplicated and enhanced by Havens and his associates, in the Army Laboratories of the Neurotropic Virus Commission established first in Cairo, Egypt, and later in this country at the Yale University School of Medicine;[34] and again later by Neefe, Stokes and Reinhold[35] of the Commission on Measles and Mumps at the University of Pennsylvania Medical School. The strain used by Havens was collected from a soldier taken ill while in action in Italy and with this strain of infectious hepatitis virus it was found that this disease could be readily produced experimentally in man by the oral route, that is, by feeding the infective feces or spraying such material into the nasopharyngeal passages. Similarly infectious hepatitis could be produced by feeding infective serum, as well as by its parenteral administration. In both instances the incubation period ranged from twenty to thirty days and infection was

induced in from 60 to 66 per cent of those tested. It was also shown in subsequent experiments that it was in the acute active stage of the disease when the virus could be detected in the blood and feces, and not in the incubation period or the convalescent period.[35, 36] To date experiments in this country which have attempted to demonstrate the virus in the nasopharyngeal washings and the urine have been negative.[36]

The evidence from experimental observations is strong that the intestinal-oral circuit is therefore one of the natural routes of spread of this disease and this, coupled with the field observations that this disease flourishes where camp sanitation is bad,[37] and that water borne infections have been described,[31, 38] is presumptive evidence that this infection should be regarded as a member of the enteric group until proven otherwise.

And finally and perhaps the most useful of discoveries in connection with the disease which has also been made by members of an Army Commission, was the discovery by Stokes and Neefe[39] that this disease could be prevented as in measles, by the injection, during the incubation period, of gamma globulin. In view of the long incubation period, presumably covering twenty-five days, infectious hepatitis is a disease which lends itself rather well to this type of passive immunization.[40] This allows for a period of about seventeen days after exposure during which the inoculation can be effective. If given within six days of the onset there is less chance of preventing an attack of the disease than if given immediately earlier. This discovery is in keeping with the idea that immune bodies develop in the disease as an expression of an immunity which is probably lasting.[41]

In summary therefore, we find that as a result of work largely carried out during the past few years the disease, *infectious hepatitis* stands on much firmer ground than it did before. The accumulation of new information has led to the identification of the causative agent as a filterable agent; to the clarification of its clinical picture; to its assignment as a member of the group of enteric infections; and to its prevention by passive immunization. From a nosological point of view it would now seem as if the term catarrhal jaundice could be eliminated from clinical literature, unless it can be shown to serve a more useful purpose than is apparent to us now. Furthermore, there is now less reason than ever to confuse infectious hepatitis with Weil's disease. As to serum jaundice and infectious hepatitis, these two seem to have much in com-

mon and it is well to keep this relationship in mind, if only for the reason that both may be artificially and inadvertently produced by transferring blood or serum from an infected to a well individual and this may even result from the use of improperly sterilized syringes.

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# THE EYE AS A GUIDE TO LATENT NUTRITIONAL DEFICIENCY DISEASES*

## *A Clinical Study of Ocular Diseases at an Advanced Base Hospital in the Southwest Pacific*

ARTHUR ALEXANDER KNAPP

Captain (MC), USNR.

OCULAR manifestations may be the first signs in systemic disease, or they may appear associated with other symptoms. In either instance the eye lesions often will suggest or decide the diagnosis. Occasionally a widespread disorder, such as arteriosclerosis, is recognized exclusively by the eye signs. These facts apply equally well to generalized pathologic conditions, viz., infections, metabolic disturbances and vitamin deficiencies.

Having already made experimental observations on changes in the eye secondary to vitamin deficiencies, I became interested in determining whether similar ocular lesions were present in a group of service men suffering from malnutrition. Among the Marine and Naval personnel with various eye complaints who during the past year had been examined in the ophthalmic department of an advanced base hospital in the Southwest Pacific, many had subsisted on a restricted diet. While no individual records are available, still the basic findings are sufficiently definite to permit certain conclusions.

The majority of these men had been in the actual front lines for periods of more than six months; they were recent evacués from Guadalcanal, New Georgia, Bougainville and other islands of the Solomon chain. Canned food had been used almost exclusively, and deficiency in several essential elements, among them vitamins and minerals, was unavoidable. This study is concerned with the eye conditions of men who had been on a limited fare for six to eighteen months.

Whenever any of these patients complained that his sight had been impaired, his visual acuity was tested and then compared with the

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corresponding data in his health record at the time of enlistment. For enrollment of these pre-Pearl Harbor men a minimum reading of 15/20 in each eye had been required. It was now found that the eyesight in a few of this group had been reduced to a marked degree.

The acuity of some eyes was 6/20 or even 5/20 with the fellow eye reading 8/20 to 12/20. It is conceivable that isolated patients might have memorized the chart for the initial visual test registered in their records, but the fact that all of these patients had noticed a real impairment in vision, and the fact that a large number of them showed the same symptom after all had been in similar circumstances, justify the findings.

In this series of service men poor sight was the major eye complaint. With the use of 6 drops of a 4 per cent solution of homatropine, one drop instilled in each eye at 10 minute intervals, and by refracting the eyes after the lapse of 20 minutes following the last drop, it was discovered that these men were myopic, both by retinoscopy and acceptance. To give them 20/20 vision, or better, a minus .25 to a minus 1.25 diopter lens was accepted. No abnormality of the crystalline lenses could be detected.

The apparent onset of this *axial myopia*, or the aggravation of a trivial degree of near-sightedness, in these nutritionally deficient men is additional evidence in support of earlier animal and human investigations made by the author.[1] Over 50 per cent of the patients with progressive myopia in these studies revealed either a reduction in the myopia or a stationary condition after the administration of vitamin D and calcium. Approximately 33 per cent had less myopia. In some individuals an actual shrinkage of the myopic eyeball had taken place.

It should be remembered that a moderate percentage of myopic persons will suffer from *night-blindness* along with short-sightedness. The indicated therapy for myopia,[2] however, may also improve the poor night-sight.

Another symptom for which a number of Navy men sought relief was "inflamed eyes." There were those who had attacks of redness of the eyes, accompanied by the annoying symptoms of itching and/or photophobia. Frequently they complained that local therapy was of no avail. Such remedies sometimes aggravated the condition. Examination disclosed the varied signs of *vernal catarrh*, but a definite diagnosis never was made unless a pathognomonic stringy discharge could be recovered. Every case seen was of the mild type. It was unusual for any patient

to state that he had suffered from similar complaints before being ordered to his current duty. It must be admitted, nonetheless, that this catarrh may have been present in some men prior to enlistment, in view of the fact that allergic conjunctivitis is so prevalent in its asymptomatic form. Still, in these patients it can be logically assumed that the vernal catarrh was not sufficiently advanced to produce symptoms until the nutritional disturbance was intensified after departure from the States. The belief that allergic conjunctivitis has a nutritional basis is not new, for observations previously published[3] established this fact. Almost every patient in this former study was benefited appreciably by the use of vitamin D and calcium in sufficient dosages.

Earlier investigators have shown that myopia, night-blindness and vernal catarrh are related entities. This being so, it is not surprising that the same therapy is of value in all of these conditions.

Of the service men who had varied ocular complaints, several were found to have slightly *hazy fundi oculi.* In this group neither vitreous or lens opacities, nor corneal or fundus disease could be demonstrated. Further examination revealed the disc with a mildly blurred margin and often with a thin peripheral rim of pallor, though rarely with a diffuse pale pink color. It was found that physiologic blind spots and central form and color vision in many of these men were normal, yet optic nerves showing such signs could not be considered healthy. The dividing line between the normal and the abnormal is always controversial. In no wise did the fundi oculi in these patients resemble those of normal persons as seen in the States, where adequate nutrition is not so difficult a problem. The hazy fundus oculi and pallor of the disc may be manifestations of a latent deficiency state; since in earlier research we found comparable lesions had developed in animals on depleted diets. These experimental ocular signs were then considered as part evidence of the deficiency.

A fair percentage of the service patients with *pallor of the optic nerve* had enlarged blind spots. In others with enlarged blind spots ophthalmoscopy revealed completely normal fundi. These two latter groups almost invariably showed signs of malaria or a focus of infection or both during this period of malnutrition. Seldom was excessive smoking and/or drinking discovered to be a cause. It was unusual to find that this *retrobulbar neuritis* was a leading symptom of multiple sclerosis. Except in the cases of multiple sclerosis, all of the other patients with

retrobulbar neuritis were cured by the specific treatment of the infection or infections brought out by thorough examination. The criteria for cure were the presence of normal blind spots, normal central form and color vision, and normal optic discs. No one whose condition was diagnosed as retrobulbar neuritis was evacuated to the United States. Complete recovery usually followed the elimination of foci of infection and/or other corrective measures, during which course of treatment nutritious food was served. It was then impossible to judge the precise factor or factors concerned in the cure—whether restoration of the optic nerve to normal was due to the disappearance of the infection or toxin, the improved nutrition, or a combination of them.

Nutritional lack, however, can play an important part in producing lesions of this type, for similar ocular findings were repeatedly induced in animals placed on inadequate diets.[4] Moreover, retrobulbar neuritis and allergic conjunctivitis may be related lesions, not coincidental ones. An underlying allergy may be responsible for both conditions.

In only a few of these subjects under consideration was a characteristic *chorioretinitis* discovered. It was an accidental finding, the inflammation not giving rise to any subjective symptoms. The condition was seen in the course of a consultation for some other irrelevant complaint. The chorioretinitis involved the macular region, though never precisely invading the fovea centralis. Vision in all cases was preserved. The pathologic area, approximately the diameter of the disc, usually consisted of a ring of small circular depigmented spots of a yellowish-pink color, and in this group all of the spots had shown activity of different degrees. They were seen in men of all ages. These patients included those who proved normal in every type of clinical investigation—general medical, nose and throat, dental, genito-urinary—and in blood and urine examinations. Their only treatment was dietary. In a few days they rapidly recovered on the diet served, mainly consisting of a variety of fresh foods: milk, eggs, fruits, meats and vegetables, infrequently fortified with a supplement of multiple vitamins. As the spots improved, the usual process was observed to take place, a proliferation of pigment at the periphery of each small pink circle. With complete healing, a sharp line of demarcation separated the healthy retina from the formerly inflamed zones.

Rarely, another type of chorioretinitis was noted—*chorioretinitis juxtapapillaris*. In this affection also the unhealthy membranes improved in a few days after the institution of a changed diet of vastly superior food, without medication.

COMMENT

The findings verify observations that have been made by others, namely, that ocular signs of systemic disease may occur before other manifestations become sufficiently evident to warrant a correct diagnosis.

In the patients considered in this report, there was a basic disturbance in metabolism of nutritional origin. Except for the chorioretinitis, each of the conditions discussed—myopia, night-blindness, vernal catarrh or allergic conjunctivitis, hazy fundus oculi, pallor of the optic disc and retrobulbar neuritis—has been shown to have an etiological dietary background, the extent of which in relation to other causative factors has not been thoroughly explored. There is no doubt, however, that malnutrition figures prominently in causation.

Those subjects exhibiting vernal catarrh, optic nerve disease and chorioretinitis responded well and quickly to the new diet when nutritional lack was a prime cause. They showed improvement within a matter of days. The progress of the myopic patients could not be followed over a long enough period of time, for months of study would have been necessary in order to draw any conclusion. Ample research, however, already has been done to establish the need for proper nutrition in myopia.

Common to all of the patients is the fact that apart from the eye signs they did not reveal any clinical evidence of malnutrition in other tissues. The men all appeared healthy. That is, the systemic deficiency was apparently latent. The eye signs were the sole manifestations of the metabolic disorder.

Similar conditions prevailed during many of our investigations on animals made in the Department of Pharmacology of the College of Physicians and Surgeons, Columbia University.[5] In one report many ocular lesions were described in groups of animals placed on diets in which definite nutrients were omitted—vitamins A, B and D—and in a further group on a low caloric intake. It was noted that "with the exception of retarded growth, the eye lesions were the first pathologic features to be observed."

Naturally, in a study of this type, no large enough groups from the same ship or compound could be observed. Neither could the dietaries furnished on the various ships, in the fields and at different bases be checked; nor could the hospital menus be analyzed carefully from a

quantitative and qualitative point of view. It may be taken for granted that the diets served at our base hospital, situated in a fine food producing country, were far superior to those received by the men at their battle stations. Particular attention was paid to the milk intake. A quart daily was advised to give the optimum of a gram of available calcium.

Frequently, the diets were also fortified with supplements of vitamins A, B, C and D. The importance of vitamin D especially was stressed, for the lack of it may be a potent cause of eye disease. Comparatively high doses of the vitamin D were prescribed for all patients with progressing axial myopia, vernal catarrh and night-blindness.

## CONCLUSION

In a group of patients in the armed forces suffering from faulty food intake, certain eye conditions have been demonstrated–axial myopia, vernal catarrh (also called allergic conjunctivitis), hazy fundus oculi, chorioretinitis and optic nerve disease. These findings further substantiate earlier animal and human research.

When there are no other clinical signs or symptoms of inadequate feeding in a patient, examination of the eyes may reveal the only evidence of malnutrition. Hence, the eye may serve as a guide to latent nutritional deficiency diseases.

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